

Virtual Mentor

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Distinguishing between Restoration and Enhancement in Neuropharmacology

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A patient comes to your office telling you that she finds herself having a bit of difficulty maintaining concentration. At 51 years old, she has a demanding job in the financial industry, is never far from either a computer or her PDA, and carries two cell phones, one for friends and family and the other for work. You give her a thorough examination (noting that she checks her PDA twice during the exam), which reveals that she is healthy and without any neurological or psychiatric dysfunction. She mentions that one of her coworkers, who is also continually bombarded by information and multitasks ferociously, went to his physician and received a drug which seemed to help him. He seems happier now and his life is less out of control. She tells you that she generally would prefer not to take drugs, but the combined demands of her job, her family, and modern life are such that she needs some kind of help, and she needs it now.

The hypothetical scenario described above is hardly uncommon. A steady stream of media reports [1] has substantially raised the public profile of the new phenomenon of cosmetic neuropharmacology—the use of drugs to modify brain function in people who have no underlying disease [2]. Even in the absence of direct-to-consumer marketing on the topic, patient requests for such drugs, particularly those that improve one or another domain of cognition, are increasingly becoming a fact of life. What does this mean for physicians?

One answer comes from the Ethics, Law and Humanities Committee of the American Academy of Neurology [3], which held a series of meetings between 2007 and 2009 to consider the question of how neurologists should respond to off-label requests by patients for neuroenhancements. Their deliberations led to a series of recommendations which can be summarized as follows:

- The prescription of drugs for neuroenhancement is not legally or ethically mandatory;
- The prescription of drugs for neuroenhancement is not legally or ethically prohibited;
- Therefore, the prescription of drugs for neuroenhancement is legally and ethically permissible.

These conclusions derive from consideration of the proper goals of medicine [4], a core domain of medical practice in which physicians are traditionally considered to be ethically obligated to act (e.g., the prevention, diagnosis, and treatment of disease). Cosmetic neuropharmacology occupies a nebulous region on the fringes of

this core domain, and thus we allow but do not require physicians to prescribe off-label cognitive-enhancement medications.

These recommendations leave the decision about prescribing enhancements firmly in control of the individual physician. The AAN committee makes one particular point that bears repeating: there are no medications specifically approved by the FDA for cognitive enhancement at the present time. It is physicians' prerogative to prescribe existing drugs off label as cognitive enhancements, but they must also grapple with all of the relevant concerns that come with off-label prescribing [5].

Providing guidance about what physicians *can* do is useful, but in the context of a busy practice, what physicians really want to know is what they *should* do. The answer, of course, depends upon the specifics of the situation, and that is why the AAN committee was correct to place the onus on physicians. What I shall do is distill some insights from the debate amongst neuroethicists regarding pharmacological cognitive enhancement in an effort to equip the practicing physician with the tools to arrive at an answer that is consistent not only with the goals of medicine but also with his or her internal moral compass.

Neuroethicists think much more about the impact of cognitive enhancement on society at large than they do about the challenges that physicians face in their day-to-day practice. Thus the four central issues that dominate neuroethical discourse are safety, noncoercion, distributive justice, and authenticity [6, 7]. While all are worthy of consideration, asking the medical profession to protect society against the social implications of cognitive enhancement seems not only quixotic but also misplaced. On the other hand, so long as cognitive enhancement is by prescription only, physicians will be the *de facto* gatekeepers.

Rather than recount the societal ills that may arrive with the widespread adoption of cognitive enhancement, it is worth considering the matter in the pragmatic terms that physicians require. To do so, I draw the reader's attention to a much-ignored issue that bears upon the physician's decision whether to prescribe a cognitive-enhancement drug—the distinction between restoration and enhancement. It is widely recognized that as people age, their cognitive abilities decline even in the absence of disease. Although not included in the *DSM-IV*, the nosological entity of age-associated memory impairment (AAMI) captures commonsense notions of this decline: individuals over age 50 have AAMI if they have no neurological or psychiatric disease and score one standard deviation below the mean of young adults on any test of memory [8].

Notable is the fact that this decline is specifically defined as normal—although there is a measurable change in cognitive function associated with aging, it is much the same as the panoply of age-related changes in muscle strength, endurance, and other forms of physical vigor which accompany normal aging. Prescribing a cognitive enhancement for a 60-year-old patient in good health who exhibits AAMI is restoring that individual's former function, while prescribing the same drug for a 25-

year-old, who is at the peak of his or her cognitive function, is enhancement (as the dilemma discussed elsewhere in this issue makes clear), a difference most people intuitively recognize.

The restoration-enhancement distinction becomes particularly relevant to the practicing physician in the context of safety—are the benefits afforded by the treatment sufficient to account for the attendant risks? The answer varies with the specific treatment under consideration and the overall health of the patient, and this is where the expertise of the physician comes into play most prominently. While physicians may have a great deal of experience with the risks that cognitive enhancements might have, it is harder to enumerate fully the benefits that such drugs may bring. The benefit that accrues to an aging individual experiencing age-associated memory impairment—restoration—differs from the benefit that accrues to a young adult. It is impossible to say whether one confers greater advantage than the other, but many physicians seem to find less discomfort with the prospect of restoring “impaired” memory than enhancing memory that is at its peak [9].

In some ways, the current situation, where physicians must decide for themselves whether to prescribe drugs off-label for cognitive enhancement, is at once easier and more difficult than the situation might be in the near future. At least three experimental compounds have met their phase II endpoints for age-associated memory impairment [10], and there is every reason to expect that one of these, or some similar compound, will be approved by the regulatory authorities in the coming decade. Once the rubicon of regulatory approval is crossed, physicians will find it much more difficult to deny cognitive enhancement drugs to patients who request them, at least for restoration of function eroded by AAMI. The unwelcome dilemmas that these interventions bring to the physician’s practice will not be any less significant because we decide to call the intervention in people over age 50 with AAMI “restoration”; assuming this scenario plays out, prescribing cognitive enhancement for younger individuals will still be off-label use. As patient interest morphs into consumer demand, cognitive-enhancement drugs seem poised to continue to raise ethical dilemmas for increasing numbers of physicians.

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